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SIAPhos: Phosphorylated Sulfonimidamides and their Use in Iridium-Catalyzed Asymmetric Hydrogenations of Sterically Hindered Cyclic Enamides

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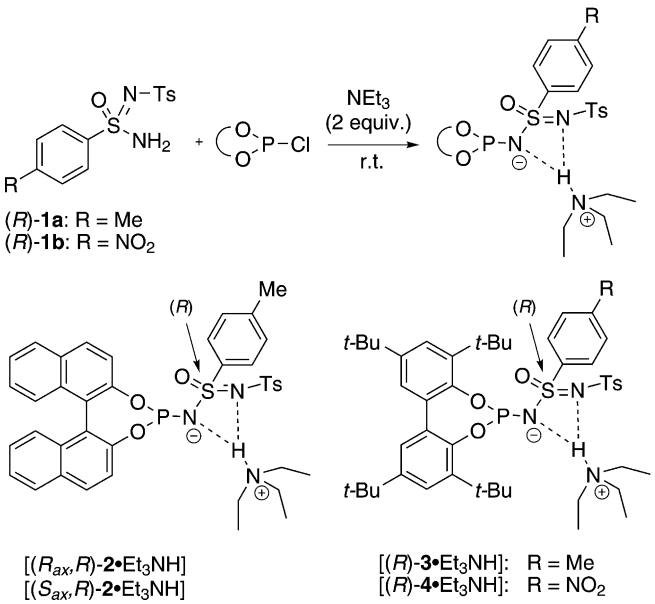
Abstract: Phosphorylated sulfonimidamides (SIAPhos) undergo ion exchange reactions with cationic complexes, $[Rh(cod)_2BF_4]$ and $[Ir(cod)_2BarF]$, or neutral complexes $[Rh(cod)Cl]_2$ and $[Ir(cod)Cl]_2$, leading to unprecedented neutral complexes with P-N-S-N chelates. Use of the resulting neutral iridium complexes in asymmetric hydrogenation reactions of tri- and tetrasubstituted enamides leads to products with high enantioselectivities (up to 92% *ee*).

Keywords: asymmetric hydrogenation; iridium; phosphorylated sulfonimidamides (SIAPhos); SIAPhos (phosphorylated sulfonimidamides); sulfonimidamides; sulfur chirality

Metal-catalyzed asymmetric hydrogenation reactions are among the most important transformations in homogeneous catalysis and, as such, have been widely studied in both academia and industry.[1] Commonly, the rhodium and iridium complexes employed in enantioselective hydrogenations of olefins are cationic because they prove more effective than their neutral counterparts.[1] This has been explained in part by the fact that the cationic metal centers display stronger bonding of the substrate compared to the analogous neutral centers, leading to a higher face discrimination.[1] Furthermore, the most successful ligands are C_2-symmetrical, so reducing the number of substrate complexes and therefore competing reaction pathways.[1,2] Because of these dogmas, neutral transition metal-based catalysts[3] and metal complexes based on ligands with C_1 symmetry[4] are somewhat undeveloped, although recent examples illustrate their potential.[3,4,5] Here, we report on the first sulfonimidamido-based phosphoramidites (SIAPhos), their rhodium and iridium complexes and the application of these neutral C_1-symmetrical complexes in asymmetric hydrogenation reactions. The iridium complexes are



Scheme 1. Synthesis of sulfonimidamide-based phosphoramidites (SIAPhos).

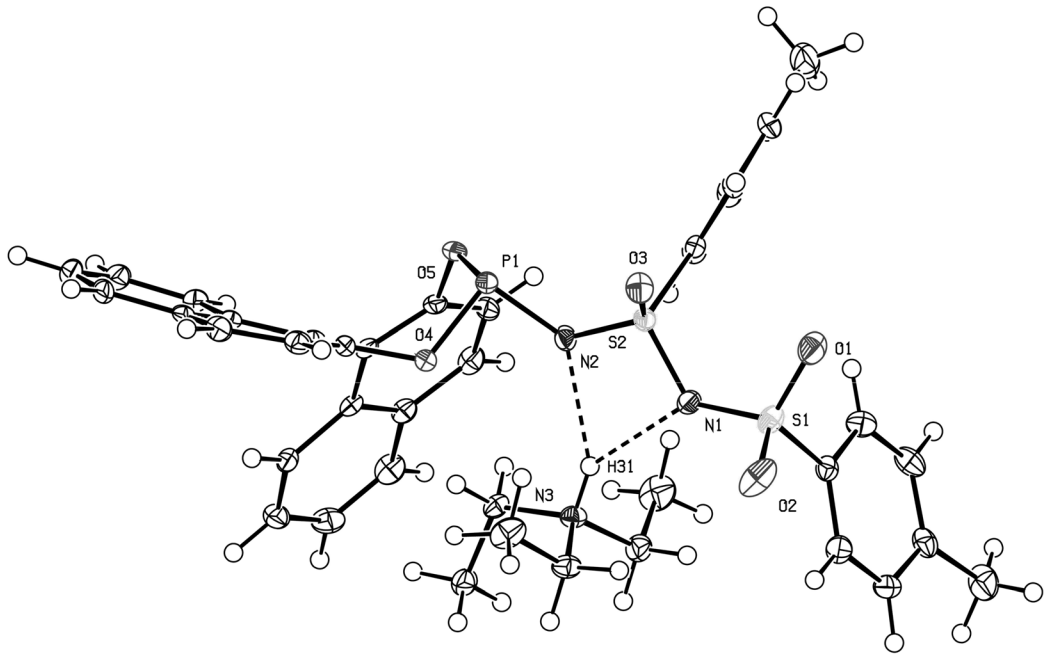


Figure 1. X-ray structure of [(R_{ax},*R*)-**2**·Et_3NH] (ORTEP view, 50% probability level), selected atomic distances (Å): H31−N3 = 0.932 (19); H31−N1 = 2.20(2); H31−N2 = 2.217(19); N2−P1 = 1.6605(18); N2−S2 = 1.5541(19); S2−N1 = 1.5844(18); N1−S1 = 1.6022(16).

very selective catalysts for sterically hindered tetra-substituted acetamido-alkenes, providing new routes to relevant products for the preparation of bioactive compounds.[6] Although the resolution of various sulfonimidamides is established,[7] their applications as chiral ligands in transition metal catalysis are still scarce. Hypothesizing that sulfonimidamides could be N-phosphorylated, we envisioned that the chemistry would be compatible with that of METAMORPhos, the sulfonamide-based analogues that we have recently introduced.[3a,8]

Sulfonimidamido-based phosphoramidites (SIAPhos) were accessible by reactions between sulfonimidamides **1** and phosphochloridites in the presence of Et_3N (Scheme 1).[9] With enantiomerically pure sulfur reagents, products **2**–**4** were obtained in almost quantitative yields with retention of chirality. The structures of [(R_{ax},*R*)-**2**·Et_3NH] and [(*R*)-**3**·Et_3NH] were confirmed by X-ray crystallography (Figure 1 and Figure 2, respectively).[9] Noticeably, in both compounds one equivalent of Et_3NH^+ is bound to the anionic core, a feature that resembles the binding mode in sulfonamido-phosphoramidites.[3a] Interestingly, in [(R_{ax},*R*)-**2**·Et_3NH] the ammonium proton is equally bound to N-1 and N-2 [2.20(0.2) and 2.22-(0.2) Å, respectively), whereas in [(*R*)-**3**·Et_3NH] the H-bond is non-symmetrical in favor of N-1 [1.95(2) *versus* 2.73(2) Å for N-2], presumably due to the steric congestion with the *t*-Bu groups.[9] The central chirality of the sulfonamido fragment in [(*R*)-**3**·Et_3NH] imposes *pseudo*-axial chirality on the *tropos* biphenol backbone [*pseudo*-(*S*) configuration in the X-ray; Figure 2]. As evidenced by the X-ray structures and solution phase ^{31}P NMR experiments, the N-phosphorylation of the sulfonimidamides had no effect on the absolute configuration at sulfur.[8]

When enantiopure [(R_{ax},*R*)-**2**·Et_3NH] was combined with [$Rh(nbd)_2BF_4$] (a common hydrogenation catalyst precursor), a single product was formed, which was identified as neutral [Rh(R_{ax},*R*)-**2**(nbd)] by NMR spectroscopy and HR-MS.[9] In this complex the ligand chelates to the metal with its P-N-S-N core forming a 5-membered ring (Scheme 2). As evidenced by the ^{31}P NMR profile (Figure 3), the complex is configurationally stable and no isomerization to the corresponding diastereomeric complex [Rh(S_{ax},*R*)-**2**-(nbd)] occurs, even after 24 h in solution (CD_2Cl_2) at room temperature. In contrast to the coordination behavior of the analogous sulfonamido-phosphoramidites,[3a] none of the sulfonimidamido-based phosphoramidites led to dimeric μ-P,N^--bridged dinuclear rhodium complexes,[3a] which can be attributed to the steric bulk of the SIAPhos ligands in combination with their chelating capability through the second nitrogen atom (N-1 in Figure 1 and Figure 2).

Interestingly, an ion exchange was also observed when [(*R*)-**3**·Et_3NH] derived from the bulky 3,3′,5,5′-tetra-*tert*-butylbiphenyl-2,2′-diol was treated with cationic [$Rh(cod)_2BF_4$] and [$Ir(cod)_2BarF$] affording the corresponding neutral complexes [Rh(*R*)-**3**(cod)] and

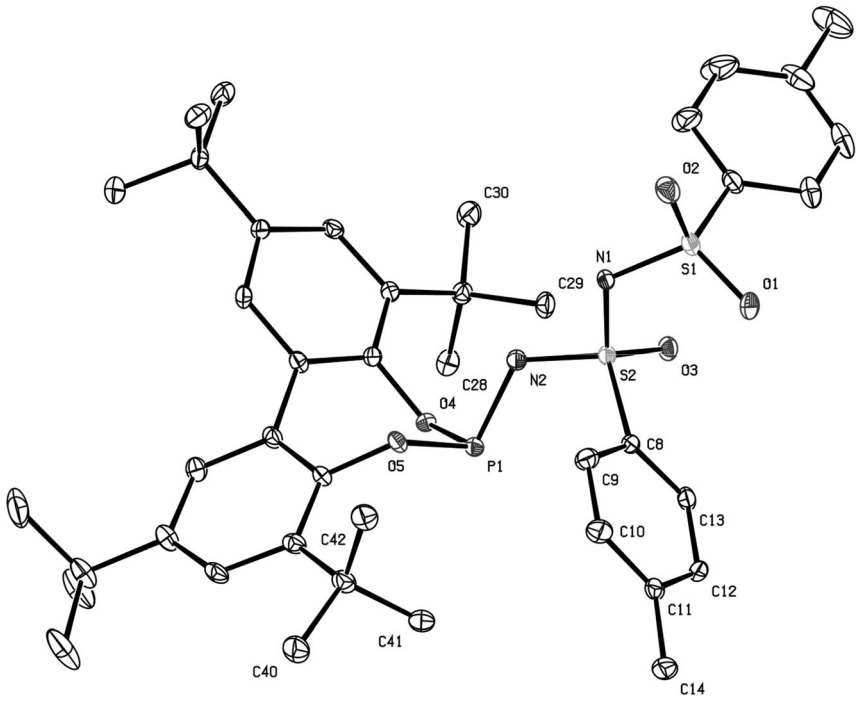
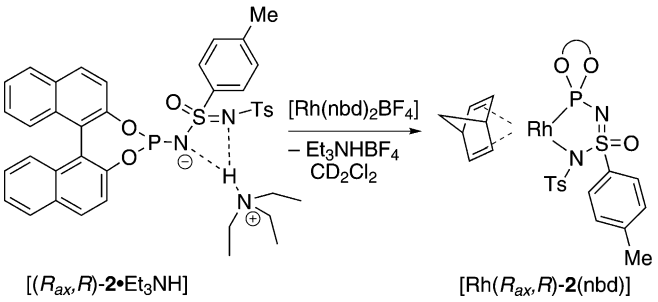


Figure 2. X-ray structure of [(*R*)-**3**·Et_3NH] (ORTEP view, 30% probability level; protons, solvent molecules and Et_3NH^+ moiety omitted for clarity), selected atomic distances (Å): N2–P1 = 1.665(2); N2–S2 = 1.543(2); S2–N1 = 1.602(2); N1–S1 = 1.6163(19); C29–O3 = 3.305(3); C41–C10 = 3.612(4); C42–C9 = 3.851(4).



Scheme 2. Treatment of [(R_{ax},*R*)-**2**·Et_3NH] with the complex $[Rh(nbd)_2BF_4]$.

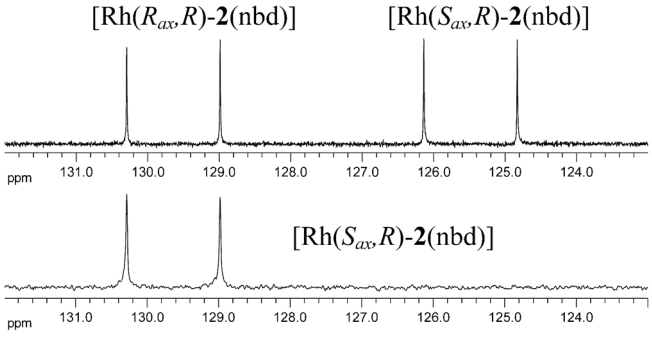
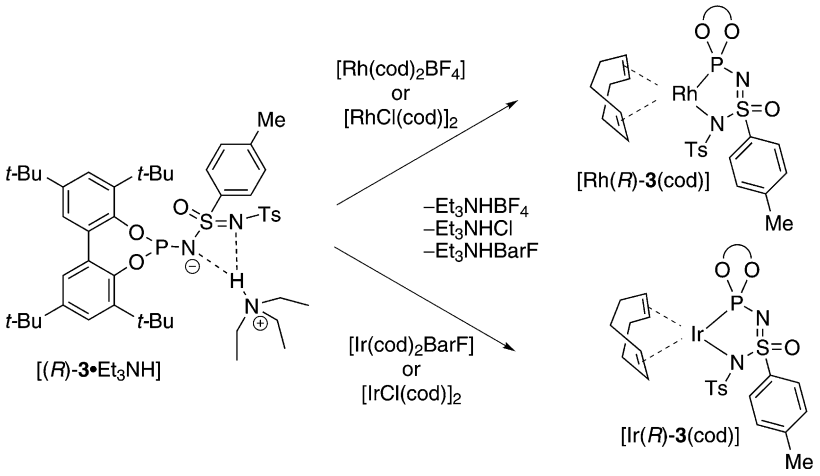


Figure 3. ^{31}P NMR profile (202.3 MHz, CD_2Cl_2) of a diastereomeric mixture of [Rh(R_{ax},*R*)-**2**(nbd)] and [Rh(S_{ax},*R*)-**2**-(nbd)] (*top*), and of diastereopure [Rh(R_{ax},*R*)-**2**(nbd)] after 24 h in solution at room temperature (*bottom*), δ (ppm) = 129.44 {d, $^1J_{P,Rh}$ = 264 Hz, [Rh(R_{ax},*R*)-**2**(nbd)]}, 125.48 {d, $^1J_{P,Rh}$ = 264 Hz, [Rh(S_{ax},*R*)-**2**(nbd)]}.

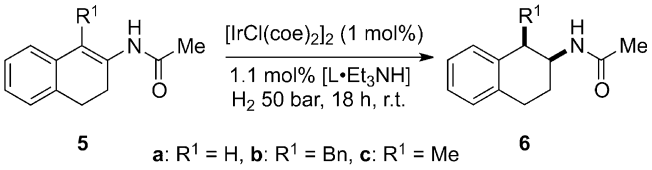
[Ir(*R*)-**3**(cod)], respectively (Scheme 3). The chelating effect of the ligand was even sufficient to instantaneously displace chloride ions from metal complexes such as $[RhCl(cod)]_2$ and $[IrCl(cod)]_2$.[9] This ion exchange behavior is remarkable because chloride is a strongly coordinating anion, and structures with μ-Cl bridges commonly require strong alkali reagents for chloride removal.

The neutral rhodium and iridium complexes were then evaluated as catalysts in asymmetric hydrogenation reactions. The most interesting results were obtained with the iridium-based systems, which did not give satisfactory results for benchmark substrates (see Supporting Information)[9] but allowed enantioselective hydrogenations of conjugated, multi-substituted cyclic enamides. Due to potential applications in the synthesis of bioactive compounds, the resulting products have synthetic relevance,[6] and generally, those transformations are reputed to be difficult. In this particular case, asymmetric hydrogenation of *N*-(3,4-dihydronaphthalen-2-yl)acetamide (**5a**) with a catalyst bearing (*R*)-**4** as ligand led to amide **6a** with a remarkable 75% *ee* (Table 1, entry 4). Also tetrasubstituted cyclic enamides reacted well affording the corresponding amides with high enantioselectivities.



Scheme 3. Treatment of SIAPhos [(*R*)-**3**·Et_3NH] with rhodium and iridium complexes.

Table 1. Hydrogenation with Ir-based SIAPhos catalysts.



5 **a**: R^1 = H, **b**: R^1 = Bn, **c**: R^1 = Me **6**

Entry	L[a]	Substrate	Conv. [%][b]	*ee* [%][b]
1	(R_{ax},*R*)-**2**	**5a**	trace	–
2	(S_{ax},*R*)-**2**	**5a**	trace	–
3	(*R*)-**3**	**5a**	>98	70
4	(*R*)-**4**	**5a**	81	75
5	(*R*)-**3**	**5b**	27	73
6	(*R*)-**4**	**5b**	55	85
7	(*R*)-**3**	**5c**	75	86
8	(*R*)-**4**	**5c**	55	92

[a] Ir: 0.5 mM in CH_2Cl_2, reaction volume: 2.5 mL.
[b] Determined by GC (for **6a** and **6c**) or HPLC (**5b**) using chiral stationary phases. From **5b** and **5c** *cis*-configured products were selectively formed. Complexes bearing (*R*)-**3** and (*R*)-**4** gave the same enantiomeric products from all three substrates.

Thus, starting from *N*-(1-benzyl-3,4-dihydronaphthalen-2-yl)acetamide (**5b**) product **6b** was obtained with up to 85% *ee* (at 55% conversion) (Table 1, entry 6), which are among the highest *ee* and conversions reported so far.[10] Hydrogenating *N*-(1-methyl-3,4-dihydronaphthalen-2-yl)acetamide (**5c**) led to amide **6c** with 92% *ee* (at 55% conversion, Table 1, entry 8), which, to the best of our knowledge, is the highest *ee* ever reported in a catalytic synthesis of this biologically relevant and challenging substrate. To our surprise, complexes with sulfonimidamido-based phosphoramidites having two stereogenic elements, but being less bulky than the 3,3′,5,5′-tetra-*tert*-butylbiphenyl-2,2′-diol-based backbones of (*R*)-**3** and (*R*)-**4**, resulted only in trace amounts of products (Table 1, entries 1 and 2).

In conclusion, we have prepared sulfonimidamido-based phosphoramidites (SIAPhos) and found them to be effective in catalyzed asymmetric hydrogenations of tri- and tetra-substituted acetamido-alkenes with neutral iridium complexes. In transformations of **5c** a product with up to 92% *ee* was obtained, which – to the best of our knowledge – is the highest enantioselectivity ever reported in a conversion of this challenging and biologically relevant substrate.[3a] Finally, we have shown that neutral iridium catalysts based on SIAPhos ligands are more effective in the asymmetric hydrogenation reaction of strongly coordinating substrates. We expect that future asymmetric transformations of likewise strongly coordinating substrates may be addressed by analogous strategies, that is, by taming the cationic character of the active metal center.

Experimental Section

General Procedure for the Asymmetric Hydrogenation of 5a–c

A 15-mL pressure reactor containing a glass insert was successively charged, under inert conditions, with a dichloromethane (DCM) solution (1 mL) of the ligand, a DCM solution (0.5 mL) of the metal precursor {either $[Rh(nbd)_2BF_4]$ or $[IrCl(coe)_2]_2$}, and a DCM solution (1 mL) of the substrate, at the required concentrations. The resulting solution was stirred at room temperature for 5 min and then exposed to 50 bar of H_2 atmosphere (at 298 K under vortex-type stirring with 300 rpm).

CCDC 746665 and CCDC 746666 contain the supplementary crystallographic data for **2** and **3**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

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References

[1] a) J. G. de Vries and C. J. Elsevier, *The Handbook of Homogeneous Hydrogenation*, Wiley-VCH, Weinheim, **2007**; b) H.-U. Blaser, B. Pugin, F. Spindler, M. Thommen, *Acc. Chem. Res.* **2007**, *40*, 1240; c) H.-U. Blaser, C. Malan, B. Pugin, F. Spindler, H. Steiner, M. Studer, *Adv. Synth. Catal.* **2003**, *345*, 103; d) I. D. Gridnev, T. Imamoto, *Chem. Commun.* **2009**, 7447; e) J. K. Whitesell, *Chem. Rev.* **1989**, *89*, 1581; f) J.-H. Xie, S.-F. Zhu, Q.-L. Zhou, *Chem. Rev.* **2011**, *111*, 1713.

[2] J. M. Brown, P. L. Evans, *Tetrahedron* **1988**, *44*, 4905.

[3] For successful neutral rhodium and iridium complexes, see: a) F. W. Patureau, S. de Boer, M. Kuil, J. Meeuwissen, P-A. B. Breuil, M. A. Siegler, A. L. Spek, A. J. Sandee, B. de Bruin, J. N. H. Reek, *J. Am. Chem. Soc.* **2009**, *131*, 6683; b) F. Giacomina, A. Meetsma, L. Panella, L. Lefort, A. H. M. de Vries, J. G. de Vries, *Angew. Chem.* **2007**, *119*, 1519; *Angew. Chem. Int. Ed.* **2007**, *46*, 1497. For analogous strategies in Ir asymmetric hydrogenation, see also: c) G. Erre, S. Enthaler, K. Junge, D. Addis, M. Beller, *Adv. Synth. Catal.* **2009**, *351*, 1437; d) S. Enthaler, G. Erre, K. Junge, K. Schröder, D. Addis, D. Michalik, M. Hapke, D. Redkin, M. Beller, *Eur. J. Org. Chem.* **2008**, 3352. For Ir asymmetric hydrogenation examples of cyclic enamides with C_2-symmetrical phosphoramidites see also: e) G.-H. Hou, J.-H. Xie, P.-C. Yan, Q-L. Zhou, *J. Am. Chem. Soc.* **2009**, *131*, 1366. For indicative examples of phosphoramidites in IrCl-based neutral catalysis, see also: f) T. Ohmura, J. F. Hartwig, *J. Am. Chem. Soc.* **2002**, *124*, 15164; g) F. Lopez, T. Ohmura, J. F. Hartwig, *J. Am. Chem. Soc.* **2003**, *125*, 3426; h) C. A. Kiener, C. Shu, C. Incarvito, J. F. Hartwig, *J. Am. Chem. Soc.* **2003**, *125*, 14272; i) A. Leitner, S. Shekhar, M. J. Pouy, J. F. Hartwig, *J. Am. Chem. Soc.* **2005**, *127*, 15506; j) G. Lipowsky, N. Miller, G. Helmchen, *Angew. Chem.* **2004**, *116*, 4695; *Angew. Chem. Int. Ed.* **2004**, *43*, 4595.

[4] For reviews, see: a) V. A. Pavlov, *Tetrahedron* **2008**, *64*, 1147; b) K. C. Bhowmick, N. N. Joshi, *Tetrahedron: Asymmetry* **2006**, *17*, 1901; c) J. Wassenaar, J. N. H. Reek, *Org. Biomol. Chem.* **2011** ,*9*, 1704; d) H. Fernandez-Perez, P. Etayo, A. Panossian, A. Vidal-Ferran *Chem. Rev.* **2011**, *111*, 2119; e) F. Boeda, T. Beneyton, C. Crévisy, *Mini-Rev. Org. Chem.* **2008**, *5*, 96; f) H. A. McManus, P. J. Guiry, *Chem. Rev.* **2004**, *104*, 4151. For some examples: g) G. Francio, F. Faraone, W. Leitner, *Angew. Chem.* **2000**, *112*, 1486; *Angew. Chem. Int. Ed.* **2000**, *39*, 1428; h) X. P. Hu, Z. Zheng, *Org. Lett.* **2004**, *6*, 3585; i) X. P. Hu, Z. Zheng, *Org. Lett.* **2005**, *7*, 419; j) Q. H. Zeng, X. P. Hu, Z. C. Duan, X. M. Liang, Z. Zheng, *Tetrahedron: Asymmetry* **2005**, *16*, 1233; k) J. D. Huang, X. P. Hu, Z. C. Duan, Q. H. Zeng, S. B. Yu, J. Deng, D. Y. Wang, Z. Zheng, *Org. Lett.* **2006**, *8*, 4367; l) D. Y. Wang, X. P. Hu, J. D. Huang, J. Deng, S. B. Yu, Z. C. Duan, X. F. Xu, Z. Zheng, *Angew. Chem.* **2007**, *119*, 7956; *Angew. Chem. Int. Ed.* **2007**, *46*, 7810; m) M. Qiu, X. P. Hu, D. Y. Wang, J. Deng, J. D. Huang, S. B. Yu, Z. C. Duan, Z. Zheng, *Adv. Synth. Catal.* **2008**, *350*, 1413; n) S. B. Yu, J.-D. Huang, D. Y. Wang, X. P. Hu, J. Deng, Z. C. Duan, Z. Zheng, *Tetrahedron: Asymmetry* **2008**, *19*, 1862; o) K. A. Vallianatou, I. D. Kostas, J. Holz, A. Börner, *Tetrahedron Lett.* **2006**, *47*, 7947; p) Y. Yan, X. Zhang, *J. Am. Chem. Soc.* **2006**, *128*, 7198; q) X. Zhang, B. Cao, Y. Yan, S. Yu, B. Ji, X. Zhang, *Chem. Eur. J.* **2010**, *16*, 871; r) Z. C. Duan, X. P. Hu, J. Deng, S. B. Yu, D. Y. Wang, Z. Zheng, *Tetrahedron: Asymmetry* **2009**, *20*, 588; s) M. Qiu, D. Y. Wang, X. P. Hu, J. D. Huang, S. B. Yu, J. Deng, Z. C. Duan, Z. Zheng, *Tetrahedron: Asymmetry* **2009**, *20*, 210; t) S. B. Yu, X. P. Hu, J. Deng, D. Y. Wang, Z. C. Duan, Z. Zheng, *Tetrahedron: Asymmetry* **2009**, *20*, 621; u) J. Wassenaar, J. N. H. Reek, *Dalton Trans.* **2007**, 3750; v) J. Wassenaar, M. Kuil, J. N. H. Reek, *Adv. Synth. Catal.* **2008**, *350*, 1610; w) J. Wassenaar, J. N. H. Reek, *J. Org. Chem.* **2009**, *74*, 8403; x) C. Darcel, D. Moulin, J-C. Henry, M. Lagrelette, P. Richard, P. D. Harvey, S. Juge, *Eur. J. Org. Chem.* **2007**, 2078; y) J. Wassenaar, E. Jansen, W. J. van Zeist, F. M. Bickelhaupt, M. A. Siegler, A. L. Spek, J. N. H. Reek, *Nature Chem.* **2010**, *2*, 417; z) J. Wassenaar, M. Kuil, M. Lutz, A. L. Spek, J. N. H. Reek, *Chem. Eur. J.* **2010**,*16*, 6509.

[5] For an indicative example of a neutral hydrogenation catalyst employing a C_1-symmetrical chiral ligand see: W. S. Knowles, M. J. Sabacky, *J. Chem. Soc. Chem. Commun.* **1968**, 1445.

[6] a) W. Tang, Y. Chi, X. Zhang, *Org. Lett.* **2002**, *4*, 1695; b) Z. Zhang, G. Zhu, Q. Jiang, D. Xiao, X. Zhang, *J. Org. Chem.* **1999**, *64*, 1774; c) J. L. Renaud, P. Dupau, A-E. Hay, M. Guingouain, P. H. Dixneuf, C. Bruneau, *Adv. Synth. Catal.* **2003**, *345*, 230; d) X-B. Jiang, L. Lefort, P. E. Goudriaan, A. H. M. de Vries, P. W. N. M. van Leeuwen, J. G. de Vries, J. N. H. Reek, *Angew. Chem.* **2006**, *118*, 1245; *Angew. Chem. Int. Ed.* **2006**, *45*, 1223; e) P. Dupau, C. Bruneau, P. H. Dixneuf, *Adv. Synth. Catal.* **2001**, *343*, 331; f) M. C. Jetter, M. A. Youngman, J. J. McNally, M. E. McDonnell, S-P. Zhang, A. E. Dubin, N. Nasser, E. E. Codd, C. M. Flores, S. L. Dax, *Bioorg. Med. Chem. Lett.* **2007**, *17*, 6160; g) M. A. Youngman, N. M. Willard, S. L. Dax, J. J. McNally, *Synth. Commun.* **2003**, *33*, 2215; h) J. Meeuwissen, M. Kuil, A. M. van der Burg, A. J. Sandee, J. N. H. Reek, *Chem. Eur. J.* **2009**, *15*, 10272.

[7] a) C. Liang, F. Collet, F. Robert-Peillard, P. Müller, R. H. Dodd, P. Dauban, *J. Am. Chem. Soc.* **2008**, *130*, 343; b) C. Liang, F. Robert-Peillard, C. Fruit, P. Müller, R. H. Dodd, P. Dauban, *Angew. Chem.* **2006**, *118*, 4757; *Angew. Chem. Int. Ed.* **2006**, *45*, 4641; c) C. Fruit, F. Robert-Peillard, G. Bernardinelli, P. Müller, R. H. Dodd, P. Dauban, *Tetrahedron: Asymmetry* **2005**, *16*, 3484; d) C. Worch, C. Bolm, *Synthesis* **2007**, 1355; e) C. Worch, C. Bolm, *Synthesis* **2008**, 739; f) S. Azzaro, L. Fensterbank, E. Lacote, M. Malacria, *Synlett* **2008**,

2253; g) C. Worch, I. Atodiresei, G. Raabe, C. Bolm, *Chem. Eur. J.* **2010**, *16*, 677. h) For an asymmetric organocatalysis, see: C. Worch, C. Bolm, *Synlett* **2009**, 2425.
[8] a) F. W. Patureau, M. Kuil, A. J. Sandee, J. N. H. Reek, *Angew. Chem.* **2008**, *120*, 3224; *Angew. Chem. Int. Ed.* **2008**, *47*, 3180. Highlight: b) H. Yamamoto, P. Li, *Synfacts* **2008**, *7*, 0721; c) P-A. R. Breuil, F. W. Patureau, J. N. H. Reek, *Angew. Chem.* **2009**, *121*, 2196; *Angew. Chem. Int. Ed.* **2009**, *48*, 2162.
[9] See the Supporting Information.
[10] For example, at 100 bar of H_2 pressure a Ru catalyst in MeOH led to full conversion and 52% *ee* at 30 °C for 20 h. For details see ref.[6e]

